ClinicalTrials.gov Registration and Reporting Final Rule (FDA Amendments Act – Section 801) FAQs

15 August 2017

Final Rule FAQs

Q: When is the effective date and compliance date of the Final Rule?

Effective Date: **18 January 2017**

Compliance Date: **18 April 2017**

Q: Which Clinical Trials are Subject to the Requirements ("Applicable Clinical Trials")?

A: Registration and results information reporting is required for any trial for which the following is true:

⇒ The study is a pediatric postmarket surveillance of a device product

OR

⇒ Study type is interventional
⇒ Primary purpose is NOT device feasibility
⇒ Studies an FDA-regulated device product

AND

⇒ One or more of the following:
- At least 1 US facility location
- Product manufactured in and exported from the US
- Conducted under an FDA IDE

OR (for Drug/Biologic)

⇒ Study type is interventional
⇒ Study phase is NOT Phase 1
⇒ Studies an FDA-regulated drug product (including biologics)

AND

⇒ One or more of the following:
- At least 1 US facility location
- Product manufactured in and exported from the US
- Conducted under an FDA IND

Q: Does my trial meet the NIH definition of a clinical trial?

1) Does the study involve human participants?
2) Are the participants prospectively assigned to an intervention (which may include placebo or other control)?
3) Is the study designed to evaluate the effect of the intervention on the participants?

4) Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

If the answer to all four questions is **yes**, then your proposed research meets the NIH definition of a clinical trial. This definition encompasses a wide range of trial types: mechanistic, exploratory/developmental, pilot/feasibility, behavioral, and more.

Q: Are any types of trials/studies exempt from the requirements?

The following types of studies are generally excluded from the registration and results submission requirements of FDAAA 801 (**non-exhaustive list**):

- ⇒ Phase 1 drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes
- ⇒ Small clinical trials to determine feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure(s) relates to feasibility and not to health outcomes
- ⇒ Trials that do not include drugs, biologics, or devices (e.g., behavioral interventions)
- ⇒ Non-interventional (observational) clinical research (e.g., cohort or case-control studies)
- ⇒ Trials that were ongoing as of 27 September 2007 and reached the Primary Completion Date (see definition) before 26 December 2007

NOTE: Trials may be subject to the Voluntary Submission provision of FDAAA 801.

Access the following hyperlinks for further guidance and specificity:

https://grants.nih.gov/clinicaltrials_fdaaa/ACTs_under_FDAAA.htm (FDAAA Decision Tree Tool - flowchart)

https://grants.nih.gov/policy/clinical-trials/definition.htm

It should be noted that ALL NIH-funded clinical trials, whether funded in whole or in part, regardless of study phase, type of intervention, or whether subject to regulation must be registered and summary results information reported to ClinicalTrials.gov.

Q: What Registration and Reporting Information is Required?

For Registration of Applicable Clinical Trials initiated before 18 January 2017:

1. **Descriptive information about the trial:**
   - ⇒ Brief Title
   - ⇒ Brief Summary
   - ⇒ Primary Purpose
   - ⇒ Study Design
   - ⇒ Study Phase (for an applicable drug clinical trial)
   - ⇒ Study Type
   - ⇒ Primary Disease or Condition Being Studied, or the Focus of the Study

- ⇒ Intervention Name
- ⇒ Intervention Type
- ⇒ Study Start Date
- ⇒ Expected Completion Date
- ⇒ Target Number of Subjects
- ⇒ Outcomes, Including Primary and Secondary Outcome Measures

2. **Recruitment information:**
   - ⇒ Eligibility Criteria
   - ⇒ Gender
   - ⇒ Age Limits
   - ⇒ Whether the trial accepts healthy volunteers
   - ⇒ Overall Recruitment Status
   - ⇒ Individual Site Status
   - ⇒ Availability of Expanded Access for those who do not qualify for enrollment in the trial and how to obtain information about such access
3. **Location/Contact information:**
   - ⇒ Name of the Sponsor
   - ⇒ Responsible Party (by Official Title)
   - ⇒ Facility Name and Contact Information (including City, State and Zip Code for each clinical trial location, or a toll-free number through which location information can be accessed)
4. **Administrative Data:**
   - ⇒ Unique Protocol Identification Number
   - ⇒ Other Protocol Identification Numbers, if any
   - ⇒ U.S. FDA IND or IDE Protocol Number
   - ⇒ Record Verification Date

For Registration of Applicable Clinical Trials initiated on or after 18 January 2017[1]:

1. **Descriptive information about the trial:**
   - ⇒ Brief Title
   - ⇒ Official Title
   - ⇒ Brief Summary
   - ⇒ Primary Purpose
   - ⇒ Study Design
   - ⇒ Study Phase (for an applicable drug clinical trial)
   - ⇒ Study Type
   - ⇒ Pediatric Postmarket Surveillance of a Device Product, for an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device Product
   - ⇒ Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study
   - ⇒ Intervention Name(s), for each intervention studied

- ⇒ Other Intervention Name(s), for each intervention studied
- ⇒ Intervention Description, for each intervention studied
- ⇒ Intervention Type, for each intervention studied
- ⇒ Studies an FDA-regulated Device Product/Drug Product
- ⇒ Device Product Not Approved/Cleared by the FDA, if any studied intervention is a device product
- ⇒ Post prior to FDA Approval/Clearance, for an applicable device clinical trial that studies at least one device product not previously approved/cleared by the FDA
- ⇒ Product Manufactured in and Exported from the U.S., if the entry for FDA IND or IDE Number indicates that there is no IND/IDE for the clinical trial, and the entry(-ies) for Facility Information include no facility locations in the U.S. or its territories
- ⇒ Study Start Date
- ⇒ Primary Completion Date
- ⇒ Study Completion date
- ⇒ Enrollment
- ⇒ Primary Outcome Measure Information, for each primary outcome measure
- ⇒ Secondary Outcome Measure Information, for each secondary outcome measure

2. **Recruitment information:**
   - ⇒ Eligibility criteria
   - ⇒ Sex/Gender
   - ⇒ Age Limits
   - ⇒ If the trial accepts healthy volunteers
   - ⇒ Overall Recruitment Status
   - ⇒ If ended prematurely, Why Study Stopped
   - ⇒ Individual Site Status
   - ⇒ Availability of Expanded Access. If available for an IND, an expanded access record must be submitted in accordance with 21 CFR 11.28(c), unless previously submitted
3. **Location/Contact information:**
   - ⇒ Name of the Sponsor
   - ⇒ Responsible Party (by Official Title)
   - ⇒ Facility Information
4. **Administrative Data:**
   - ⇒ Unique Protocol Identification Number
   - ⇒ Secondary ID
   - ⇒ U.S. FDA IND or IDE Number
   - ⇒ Human Subjects Protection Review Board Status
   - ⇒ Record Verification Date
   - ⇒ Responsible Party Contact Information

[1] ***Subsets of the above elements are required for Pediatric Postmarket Surveillance of a Device Product that is <u>not</u> a clinical trial and for Expanded Access Records.***

For Reporting Results of Applicable Clinical Trials where the Primary Completion Date is before 18 January 2017 (if collected)[1]:

Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with 42 CRF 11.54, if the Applicable Clinical Trial studies a drug, biological, or device product that is approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit results information, as follows:

1. **Demographic and baseline characteristics of patient sample**
   ⇒ A table of the demographic and baseline data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial, including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.
2. **Primary and secondary outcomes**
   ⇒ The primary and secondary outcome measures and a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial, including the results of scientifically appropriate tests of the statistical significance of such outcome measures.
3. **Point of contact**
   ⇒ A point of contact for scientific information about the clinical trial results.
4. **Certain agreements**
   ⇒ Whether there exists an agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of participants) between the sponsor or its agent and the principal investigator (unless the sponsor is an employer of the principal investigator) that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.
5. **Serious adverse events**
   ⇒ A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial.
6. **Frequent adverse events**
   ⇒ A table of anticipated and unanticipated adverse events that are not included in the table described above that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial.

   ⇒ **If the Applicable Clinical Trial studies a drug, biological, or device product that is *not* approved, licensed, or cleared as of the Primary Completion Date, then the responsible party is *not* required to submit results information.**

For Reporting Results of Applicable Clinical Trials where the Primary Completion Date is on or after 18 January 2017 (if collected)[1]:

Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with 42 CRF 11.54, if the Applicable Clinical Trial studies a drug, biological, or device product, then the responsible party is required to submit results information, as follows:

1. **Participant Flow:**
   ⇒ Information documenting the progress of human subjects through a clinical trial, by arm, including the number who started and completed the trial. This includes the following elements:
      - Participant Flow Arm Information
      - Pre-assignment Information
      - Participant Data
2. **Demographic and Baseline Characteristics:**
   ⇒ Information documenting demographic and baseline measures and data collected by arm or comparison group and for the entire population of human subjects who participated in the clinical trial. This includes the following elements:
      - Baseline Characteristics Arm/Group Information
      - Baseline Analysis Population Information
        - Overall Number of Baseline Participants
        - Overall Number of Units Analyzed
        - Analysis Population Description
      - Baseline Measure Information
        - Name and Description of the Measure
        - Measure Type and Measure of Dispersion
        - Unit of Measure
      - Baseline Measure Data
      - Number of Baseline Participants (and Units) by Arm or Comparison Group and Overall, if different from the Overall Number of Baseline Participants or Overall Number of Units Analyzed

Information in Section 2 above generally encompasses Age, Sex and Gender, Race or Ethnicity, as well as other measures that were assessed at baseline and are used in analysis of primary outcome measures.

3. **Outcomes and Statistical Analyses:**
   ⇒ Information for each primary and secondary outcome measure by arm or comparison group, including result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any. This includes the following elements:
      - Outcome Measure Arm/Group Information
      - Analysis Population Information
        - Number of Participants Analyzed
        - Number of Units Analyzed
        - Analysis Population Description
      - Outcome Measure Information
        - Name of the Specific Outcome Measure

- Description of the Metric Used to Characterize the Specific Outcome Measure
- Time point(s) at which the Measurement was Assessed for the Specific Metric
- Outcome Measure Type
- Measure Type and Measure of Dispersion or Precision
- Unit of Measure

- Outcome Measure Data
- Statistical Analyses

4. Adverse Event Information:

⇒ Information to describe the methods for collecting Adverse Events during an Applicable Clinical Trial:

- Time Frame – The specific period of time over which AE information was collected and for which information is submitted
- AE reporting description (if the AE information collected in the clinical trial is collected based on a different definition of AE and/or SAE from that used in Final Rule)
- Collection approach used to collect AE information, whether systematic or non-systematic

⇒ Information for completing three tables summarizing anticipated and unanticipated AEs collected during an Applicable Clinical Trial:

- Table of all SAEs grouped by organ system, with the number and frequency of each event by arm or comparison group
- Table of all AEs, other than SAEs, that exceed a frequency of 5% within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group
- Table of all-cause mortality, with the number and frequency of deaths due to any cause by arm or comparison group (= all cause deaths)

⇒ Information for each table specified above must include the following elements, unless otherwise specified:

- Adverse Event Arm/Group Information
- Total Number Affected. The overall number of human subjects affected, by arm or comparison group, by:
  - SAEs
  - AEs other than SAEs that exceed a 5% frequency within any arm of the clinical trial
  - Deaths due to any cause
- Total Number at Risk. The overall number of human subjects included in the assessment, by arm or comparison group, for:
  - SAEs
  - AEs other than SAEs that exceed a 5% frequency within any arm of the clinical trial
  - Deaths due to any cause

- Adverse Event Information. For the two tables described directly above, a description of each type of SAE and other AE that is not an SAE and exceeds a frequency of 5% within any arm of the clinical trial, consisting of the following attributes:
  - Descriptive term for the AE
  - Organ system associated with the AE
- Adverse Event Data. For the two tables described above, and for each AE listed IAW the Adverse Event Information above:
  - Number of human subjects affected by such AE
  - Number of human subjects at risk for such AE

5. **Protocol and Statistical Analysis Plan (SAP):**
   ⇒ A copy of the approved protocol and the SAP (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board before the time of submission and that apply to all clinical trial Facility Locations
   - To be submitted at time of results information reporting (option to submit earlier)
   - ICFs are optional
6. **Administrative Information:**
   ⇒ Results Point of Contact for scientific information about clinical trial results information:
   - Name or official title of the Point of Contact
   - Name of the affiliated organization
   - Telephone number and email address of the Point of Contact
7. **Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products**

[1] ***Subsets of the above elements are required for Pediatric Postmarket Surveillance of a Device Product that is <u>not</u> a clinical trial.***

<u>Q: What are the requirements for updating clinical trial registration information once a Human Subjects Review Board approves a protocol amendment?</u>

For applicable clinical trials initiated on or after 18 January 2017, or for which registration information was voluntarily submitted pursuant to 42 CFR 11.60(c), if a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, updates to any relevant clinical trial registration information data elements must be submitted <u>no later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board</u>. If there is more than one human subjects protection review board for a multi-site trial, the date of the first board approval for the amendment should be used.

<u>Q: What other registration updates are required to be made to Applicable Clinical Trials in ClinicalTrials.gov?</u>

Responsible Parties should update their records in ClinicalTrials.gov **within 30 days** of a change to any of the following:

⇒ "Recruitment Status" and "Overall Recruitment Status"
⇒ "Primary Completion Date" and "Completion Date"

Other changes or updates to the record, such as protocol amendments, must be made at least every 12 months. It is recommended that the "Record Verification Date" be updated at least every 6 months for studies that are not yet completed, even if there were no changes to the record.

Q: Is a protocol and statistical analysis plan (SAP) required to be submitted?

The regulations require a copy of the protocol and SAP (if not included in the protocol) to be submitted as part of clinical trial results information for those applicable clinical trials with a Primary Completion Date on or after 18 January 2017. The submission of a protocol and SAP is not required for those applicable clinical trials with a Primary Completion Date before 18 January 2017.

Q: Must applicable clinical trials with no external sources of funding ("unfunded" studies) be registered in ClinicalTrials.gov?

Applicable clinical trials with no external sources of funding are not excluded from the requirements described in FDAAA 801. In general, an unfunded study should be registered by the Sponsor. When an investigator is considered the Sponsor (e.g., a Sponsor-Investigator), the study should be registered by the investigator's affiliated institution with the Responsible Party indicated as Sponsor-Investigator. ClinicalTrials.gov will then display the investigator as the Sponsor instead of the investigator's institution.

Q: How should results information be submitted for applicable clinical trials that are terminated prior to completion, or otherwise stopped prematurely, and for which no data were collected for one or more Outcome Measures?

If no participants were ever enrolled, the Overall Recruitment Status in ClinicalTrials.gov should be set to "Withdrawn." No results information will need to be submitted.

For trials that were terminated after participants were enrolled, any available data should be provided. If no data are available for any of the Outcome Measures, zero ("0") should be specified for the "Number of Participants Analyzed in each Arm/Group" and the data fields should be left blank. An explanation should be provided in the "Analysis Population Description" to indicate why no participants were analyzed and, if appropriate, information should be provided in the "Limitations and Caveats" module. Even if data are not entered for Outcome Measures, available data for the enrolled participants should be included in the "Participant Flow, Baseline Characteristics, and Adverse Events" modules.

Investigator and coordinator FAQ's

1. ***Should you register your research project with ClinicalTrials.gov***
   YES, Register your study at the NIH website, ClinicalTrials.gov.

   YES, if you want to publish the results of your study
   If you wish to publish your study in a peer-reviewed journal, then it is highly likely that the journal will expect your study to have been registered with ClinicalTrials.gov. Thousands of journals have adopted the policy of the International Committee of Medical Journal Editors (ICMJE) that requires registration in a publicly available register.

   YES, because in some cases, IT'S THE LAW
   A small subset of studies is required by law to be registered with ClinicalTrials.gov. The FDA Amendments Act (FDAAA) of 2007 required that most prospective studies involving regulated drugs, biological products, and medical devices must be registered on ClinicalTrials.gov. The law also requires reporting of "basic results" and adverse events for a subset of these studies. In addition, **ALL NIH-funded** clinical trials, whether funded in whole or in part by the NIH, regardless of study phase, type of intervention, or whether subject to regulation, must be registered and summary results information reported to ClinicalTrials.gov.

2. ***When do I have to register my study?***
   ICMJE requires that you register prior to enrollment of your first study participant. The law (i.e., Final Rule (42 CFR Part 11) requires that a study be registered within 21 days of enrollment of the first participant. In accordance with the Final Rule (42 CFR Part 11), you must also update your CT.gov records at least every 12 months, or within 30 days of a change in recruitment status.

3. ***When do I have to post basic results?***
   The law requires that a subset of basic information be posted on ClinicalTrials.gov for any study in which the study product is approved for any use. For example, if you are studying an approved drug for a new use, you must register basic results. You must post this information within 12 months of the "Primary Completion Date" – defined by CT.gov as the final data collection point for the primary endpoint. Please note that you may not wait until complete data analysis of your project is completed to post basic results, if such completion falls outside the required time frame.

4. ***What are the consequences if I don't register?***
   The consequences for non-compliance can include fines from the FDA or NIH, or the withholding of grant funds for you individually or for the entire institution. Other consequences include rejection for publication in top journals (even for studies not required by law to register).

5. ***What Are the Penalties for Failing to Register?***
   According to the FDA/NIH (Food and Drug Amendments Act of 2007): Penalties may include civil monetary penalties up to $10,000 fine for failing to submit or for submitting fraudulent information to ClinicalTrials.gov. After notification of noncompliance, the fine may go up to $10,000 per day until resolved. For federally funded grants, penalties may include the withholding or recovery of grant funds.

According to the ICMJE: Unregistered trials will not be considered for publication in journals that adhere to ICMJE standards. This penalty has not changed over time.